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Title of Grant: Image-based Multi-scale Modeling Framework of the Cardiopulmonary System: Longitudinal Calibration and Assessment of Therapies in Pediatric Pulmonary Hypertension

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Abstract Text

Multiscale modeling of pulmonary hypertension using Fluid-Solid-Growth formulations

Background and Objectives: Pulmonary Hypertension (PAH) is a complex disorder associated with elevated pulmonary arterial pressure and pathologies in the pulmonary arteries. Progressive thickening and/or stiffening of distal pulmonary vessels yield to an increase in pulmonary arterial pressure which can lead to fatal right heart failure. The objective of this study is to develop a Multiscale Model of the cardio-pulmonary system that accounts for both hemodynamics, and tissue growth and remodeling. From a translational perspective, the model will assist with patient stratification based on mechanistic markers (parameters), and will provide a framework on which to virtually test the performance of pharmacological interventions.

Methods: The cardio-pulmonary circulation is a system which can be divided in three components: heart, large vessels, and microvasculature. From a modeling perspective, we deal with multiscale problems in space (e.g., mesoscale & macroscale phenomena) and in time (e.g., stimuli acting in short time scales resulting in tissue changes over the long-time scales). There are two basic modeling frameworks: Finite Elements for the representation of the hemodynamics in the short time scale, and Mixture Theory for studying growth and remodeling (G&R) of the mesoscale constituents of the vessel wall.

- Hemodynamics modeling: We use fluid-solid interaction formulations [1], and a coupled multidomain approach for incorporating outflow impedance boundary conditions, reflecting structure and geometric properties of the distal vascular networks. The proximal vessels and the heart are reconstructed from medical image data. Hemodynamics in the distal networks are characterized using Womersley's theory of pulsatile flow in elastic vessels.
- Tissue G&R: Mixture theory formulations are used to track the evolution of the different mesoscale constituents of the vessel wall, namely elastin and collagen fibers and smooth muscle cells. A key component of G&R analyses is the definition of a homeostatic state, in which there is an equilibrium between the bio-chemo-mechanical stimuli (e.g. pressure, wall shear stress, nitric oxide, etc.) and the production and removal of constituents.
- Fluid-Solid-Growth (FSG) is the modeling framework which combines hemodynamics and growth and remodeling tools [2]. We are currently expanding the capabilities of this FSG framework, focusing primarily on two aspects: i) Generalization of homeostatic states for a full arterial tree, using extended Murray's law [3] considerations; ii) Development of a formal 'multiscale in time' modeling paradigm

to rigorously link stimuli in short time scales with tissue remodeling responses over the long time scales.

Current Results: We have studied hemodynamics and vessel wall mechanics in the pulmonary vasculature of a PAH patient and a normal subject [4]. Model parameters, consisting of linearized stiffness of the large vessels and Windkessel parameters for each outflow branch, were calibrated against in vivo measurements of pressure, flow and vessel wall deformation. The analysis suggests that the remodeling of distal vasculature contributes more to the increase in arterial pressure than the remodeling of proximal vasculature.

Bi-directional interactions between the heart and the vasculature play a critical role in the proper functioning of the cardiovascular system. We have developed a computational workflow [5] that incorporates finite element models of the left ventricle (LV) and the aorta to elucidate ventricular—arterial coupling in the systemic circulation. We showed that the model predictions of (1) LV pressure—volume loop, (2) aortic pressure—diameter waveforms and (3) aortic, LV, and left atrium pressure waveforms are consistent with the physiological measurements found in healthy human.

References

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